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# Evaluation of posterior reversible encephalopathy syndrome from different aspects: What is the role of serum LDH and albumin level in pathogenesis?

Ayse Guler, Seyma Ciftci, *Cenk Eraslan, Nese Celebisoy, Hadiye Sirin

*Department of Neurology and *Department of Radiology, Ege University School of Medicine, Izmir, Turkey*

### *Abstract*

*Background:* Posterior reversible encephalopathy syndrome (PRES), is characterized by headache, lethargy, visual complaints and epileptic seizures. Brain imaging findings include abnormalities of the white matter and the grey matter.The diagnosis currently relies on clinical manifestations and typical neuroimaging findings. Different pathophysiological factors can play role in the disease process. The purpose of this study is to review causes, clinical aspects, imaging-laboratory findings and prognosis in patients diagnosed with PRES. *Method:* Patients who showed clinical and magnetic resonance imaging (MRI) findings consistent with PRES between January 2011 and December 2014 were included in the study. Patient data were collected retrospectively from hospital records.
*Results:*Total number of patients was 22 (18 female, 4 male). Median age was 28 years (range 18-84). Comorbid conditions included eclampsia (n=10, 45%), pre-eclampsia (n=1, 4.5%), HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome (n=1), primary kidney disease (n=3, 13%). Acute elevation of blood pressure was found in 9 patients (40%). Five patients (22%) were using steroids or immunosupressive drugs. Typical PRES imaging pattern with bilateral parieto-occipital involvement was present in 15/22 patients (68%) and occipital involvement was present in 3/22 patients (14%). Atypical neuroimaging features included frontal involvement in 10 patients (45%), basal ganglia gray matter lesion in 1 patient (4%) and the cerebellum was involved in 3 patients (14%). Serum LDH level was high in 13 patients (59%). Hypoalbuminemia was detected in 12 patients (54%).
*Conclusion:* Although hypertension is thoughtto be the main pathologic factor in the disease process, endothelial dysfunction seems to be equally important.

## INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is an acute, rapidly evolving neurological conditioncharacterizedbytypical neuroimaging features. Magnetic resonance imaging (MRI) abnormalities described in patients with PRES include reversible subcortical vasogenicedema, typically without infarction, that preferentially affects posterior brain regions symmetrically.[1] PRES can be seen in patients at any age, with mean age ranges from 39 to 47 years across case series.[1] Clinical manifestations include encephalopathy, seizures, headache, nausea, vomiting and abnormalities of visual perception.[2,3] Conditions most commonly associated with PRES are hypertension, eclampsia, immunsupressive medication and autoimmune diseases.[4] A combination of suggestive clinical manifestations and radiological findings establishes the diagnosis of PRES. In doubtful cases, the clinical and radiological improvement that occurs once appropriate treatment is given confirms the diagnosis.[1] Immediate recognition and correction of the causative factor that provokes PRES is the best way for treatment and prevention of irreversibility.[3,5]

There are several studies in the literature about PRES dealing with clinical and neuroimaging findings, etiological factors and prognosis. However, the pathophysiological mechanisms have been discussed in only a few. The aim of the present study was to evaluate and discuss PRES in terms of clinical features, neuroimaging findings, etiological factors and prognosis as well as possible pathopysiological processes.

## METHODS

Twenty-two patients with the diagnosis of PRES,who were treated in our Neurological Intensive Care Unit at the Ege University

*Address correspondence to:* AyseGuler, M.D., Ege University School of Medicine, Department of Neurology, Bornova, 35100, Izmir, Turkey. Tel: +905338171876, e-mail: ayse.guler@ege.edu.tr, aguler7576@hotmail.com

Medical School Departmentof Neurology, between January 2011 and December 2014, were studied retrospectively. The diagnosis of PRES was made by ICU neurologists according to typical radiological findings (variable degrees of reversible vasogenic edema often with symmetrical involvement of the parietal and occipital lobes due to vascular cerebral dysregulation) and neurological symptoms including headache, visual disturbances, altered mental functioning and seizures, with an underlying etiology such as hypertension and use of immunosuppressant. MRI and the clinical course of each patient was reviewed by a neurologist and neuro-radiologist to confirm the diagnosis.

At the initial stage, demographic data, clinical presentations, co-morbid diseases, duration of hospital stay, resolution time of triggering factors, blood pressure and mean arterial pressure (MAP) were evaluated. Laboratory dataincluding serum lactate dehydrogenase (LDH) and serum albumin levelswere also collected. Plasma albumin levels below 3.5 mg/dl and LDH levels above 500 U/L wereaccepted as abnormal.

MRI was performed at our institution with 1.5 TESLA and 3.0 TESLA MRI scanners. Scanning protocol included axial T1WI, T2WI, FLAIR, diffusion-weighted imaging (DWI) and cranial apparent diffusion coefficient (ADC). The brain regions were divided into three parts: anterior circulation (including frontal, temporal and parietal lobes), posterior circulation (including occipital lobe, cerebellum and brain stem) and deep structures (including basal ganglia and deep white matter). Cranial MRI was performed twice, firstly at hospital admission and secondly during clinical follow up. MR images were also reviewed with respect to other complications such as subarachonid and cerebral hemorrhage. All MRI findings were reviewed by a neurologist and a neuroradiologist.

Blood pressure at admission was graded as normal, mean arterial pressure (MAP)≤ 105 mmHg; slightly elevated, MAP=106-115 mmHg; or significant hypertension, MAP≥116 mmHg. Treatment options to control suspected causative factors were initiated promptly. These were aggressive blood pressure control for hypertension, withdrawal of immunsuppressive agents, caesarean section for pregnant women and dialysis for chronic renal failure patients.

Disability was evaluated using the mRS (Modified Rankin Scale). mRS was measured at discharge from hospital. Level 0-3 of mRS was interpreted as a good outcome and level 4-6 as a bad outcome.

## RESULTS

### *Demographic data and co-morbid conditions*

Demographic data and co-morbid conditions are summarized in Table 1.

### *Clinical presentations, laboratory data, hospital stay and prognosis*

In the acute stage, decreased level of consciousness (consciousness alteration ranging from drowsiness to stupor and coma) was detected in 14 patients. EEG findings in these patients can indicate the presence of encephalopathy (background activity frequency under 8-9 Hz and presence of focal sharp waves). Visual loss was present in 4 and hemiparesis in 4 patients. Thirteen patients presented with epileptic seizures and one of them presented with convulsives tatus epilepticus. Table 2 summarizes the clinical presentations and co-morbid conditions.

Mean MAP was measured with non invasive procedures and was calculated by (2xdiastolic) +

**Table 1: Demographic data andco-morbidconditions of the study patients**

| | | |
|---|---|---|
| **Gender** | Male | 4 patients (18%) |
| | Female | 18 patients (82%) |
| **Age** | Median age | 28 (18-84 years) |
| **Co-morbid conditions** | Eclampsia | 10 patients (45%) |
| | Immunosuppressive therapy | 6 patients (27%) |
| | Acute renal failure | 2 patients (9%) |
| | Chronic renal failure | 1 patient (4%) |
| | Preelampsia | 1 patient (4%) |
| | HELLP syndrome | 1 patient (4%) |
| | Hypertension | 1 patient (4%) |

**Table 2: Presenting symptoms of the PRES, comparing eclampsia/pre-eclampsia versus other causes**

| Symptoms | Eclampsia/Pre-eclampsia (no. of patients) | Other causes (no. of patients) |
|---|---|---|
| Encephalopathy | 7 | 7 |
| Seizures | 9 | 4 |
| Visual impairment | 3 | 1 |
| Hemiparesis | 2 | 2 |

systolic/3 formula. During the acute stage MAP was 111 mmHg (range 85-175 mmHg). Eleven patients had no elevated MAP, 6 had slightly elevated MAP and 5 patients had significant hypertension. In this significant hypertension group, eclampsia was the etiologic factor in 3 patients, pre-eclampsia in 1 patient and acute renal failure in 1patient. Two patients with elevated MAP had a history of hypertension. Patients using immunodepressive drugs had normal MAP at the acute stage. These findings were shown in Table 3.

Serum LDH levels were high in 13 patients at admission. In 4 patients, these ranged from 500 to 800 IU and in 9 patients they were over800 IU. In 9 of the 13 patients, eclampsia/pre-eclampsia was the main etiologic factor. In 6 patients with eclampsia, LDH levels were above 800 IU. Two other patients with acute renal failure and 2 patients using immunosuppressive drugs had elevated LDH levels. These are shown on Table 4. Eight patients with elevated LDH levels also had elevated MAP. Hypoalbuminemia was detected in 12 patients at the acute stage. Serum albumin levels were not studied in 5 patients.

Median duration of hospital stay was 7.5 days (range 1-46 days). Ten patients were hospitalized longer than 8 days. Four of these patients were on immunosuppressing agents, 2 had acute renal failure and 2 had eclampsia. In these patients, co-morbid factors and multi-organ involvement were the main cause of long hospital stay. Median time to causative-factor control was 1 day (range 1-30 days). In 21 patients (95%), mRS was 0 (no symptoms) and in 1 patient (4%), it was 6.

*Neuroimaging findings and prognosis*

Cranial MRI was performed on all patients. Cerebral subcortical white matter involvement was found in 18 patients. There were no MRI lesions in 4 patients. Typical PRES imaging pattern with bilateral parieto-occipital involvement was present in 15 patients (68%) and unilateral occipital involvement was present in 3 patient (14%). Atypical neuroimaging features included frontal involvement in 10 patients (45%), basal ganglia gray matter lesionsin 1 patient (4%) and cerebellar involvement in 3 patients (14%). All these atypical lesions were seen with the usual pattern of parieto-occipital involvement. There were 15cases (68%) who had both anterior circulation and posterior circulation involvement, 3 cases (14%) had posterior circulation and 1 patient (4%) had deep structure sinvolvement. Figure 1 shows some examples of our patients MRI findings on DWI, ADC and FLAIR sequences.

Median imaging time from admission to MR imaging was 2 days (range 1-8 days). Vasogenic edema was defined on DWI as either hypo, iso or slight hyperintensity with hyperintensity on the ADC map. Fourteenpatients (64%) had this neuroimaging pattern. One patient (4%) had cytotoxic edema (hyperintesity on DWI and hypointensity on ADC) with vasogenic edema. In 3 patients (14%), hyperintesity on T2WI and

**Table 3: Mean arterial pressure (MAP) of the patientswith PRES during the acute stage**

| | All (no. of patients) | Eclampsia/pre-eclampsia (no. of patients) | Othercauses (no. of patients) |
|---|---|---|---|
| MAP ≤ 105 | 11 | 4 | 7 |
| MAP 106-115 | 6 | 4 | 2 |
| MAP≥ 116 | 5 | 4 | 1 |

**Table 4: Serum LDH level in patients groups with PRES**

| | All (no. of patients) | Eclampsia/Pre-eclampsia (no. of patients) | Other causes (no. of patients) |
|---|---|---|---|
| LDH<500 | 9 | 3 | 6 |
| LDH 500-800 | 4 | 3 | 1 |
| LDH>800 | 9 | 6 | 3 |

DWI was present, but on ADC there was no lesion. On MRI, 2 patients had intraparanchymal hemorrhage located within the cerebral convexity at a location identical to edema and the same finding was detected in another patient at control imaging performed 3 days later. These patients underwent MR venography to rule out venous sinus thrombosis. One patient who had intraparanchymal hemorrhage at the initial MRI had elevated MAP (172 mmg/Hg) and low platelet count (100,000/mm$^3$); the other had normal MAP and low platelet count (102,000/mm$^3$). Follow-up MRI was performed on 10 patients (45%). The median time between the two images was 10 days (range 1-60 days). Residual lesions on MRI were seen in 4 patients (18%).

## DISCUSSION

In 1996 Hinchey *et al*.[3] first described reversible posterior leukoencephalopathy syndrome (RPLS), defining a distinctive syndrome usually associated with hypertensive encephalopathy, eclampsia, uremia, porphyria and immunosuppressant toxicity. In 2000 Casey *et al*.[6] studied neuroimaging findings of this syndrome and proposed the term posterior reversible encephalopathy syndrome (PRES) for RPLS, to stress the common involvement of the both the grey and the white matter. The clinical symptoms include headache (58%),altered alertness (92%),abnormalities of visual perception (39%) andseizure (87%).[7] In the present study, seizures and altered alertness were the most common symptoms.

PRES preferentially affects women and relatively young individuals with serious co-morbidities.[7] In the present study, hypertension with eclampsia/pre-eclampsia was the most common comorbid disease, and the second most common was the usage of immunosuppressive drugs including cyclosporin and corticosteroids.

PRES has been increasingly observed in patients on immunosuppressive therapy or chemotherapy and in patients with infection, sepsis and shock without elevation of systemic

**Table 5: Lesion distrubution on MRI of patients with PRES in relation to hypoalbuminemia, serum LDH level and mean arterial pressure**

| | Total number of patients | AC | PC | DS | AC+PC | AC+PC+DS |
|---|---|---|---|---|---|---|
| **Hypoalbuminemia** | 12 | 0 | 2 | 0 | 9 | 1 |
| **LDH level** | | | | | | |
| >800 U* | 9 | 0 | 0 | 0 | 6 | 1 |
| 500-800 U | 4 | 0 | 0 | 0 | 4 | 0 |
| <500 U** | 9 | 0 | 2 | 0 | 5 | 0 |
| **Mean arterial pressure** | | | | | | |
| ≥116 mmHg*** | 5 | 0 | 1 | 0 | 1 | 1 |
| 106-115 mmHg | 6 | 0 | 1 | 0 | 5 | 0 |
| ≤105**** | 11 | 0 | 1 | 0 | 8 | 0 |

AC: anterior circulation, PC:posterior circulation, DS:deep structures
* 2 patients had no any MRI lesions on imaging
**2 patients had no any MRI lesions on imaging
*** 2 patient had no any MRI lesion on imaging
**** 2 patients have no any MRI lesions on imaging

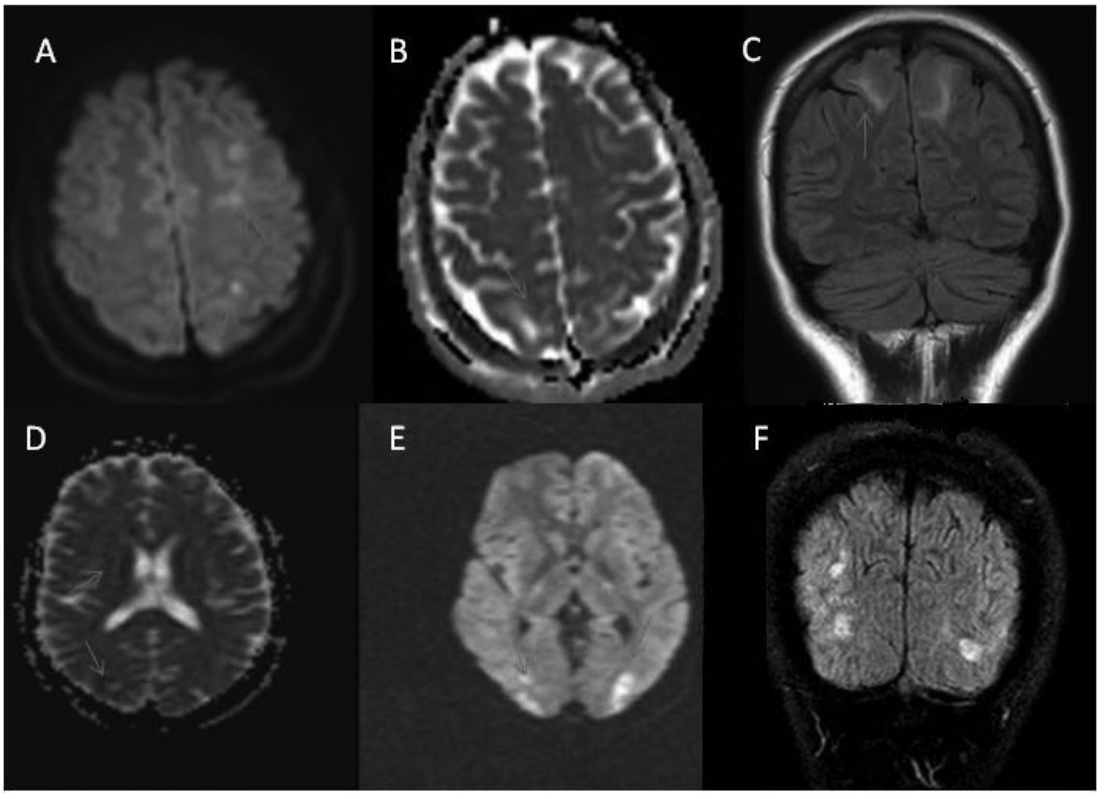


Figure 1. Cranial MRI findings on DWI(A, E), ADC(B,D) and FLAIR(C,F) sequences(blue arrows shows lesions)

blood pressure. In the present study, approximately 45% of patients had normal MAP and patients using immunosuppressive agents all had normal MAP. A proinflammatory systemic process, as has been reviewed recently by Bartynski, may be occurring in the majority of patients.[5] Endothelial injury is associated with thrombocytopenia, schistocytes and increased LDH. Cytokines up-regulate endothelial surface antigens and increased leukocyte adherence (trafficking) leads to microcirculatory dysfunction. Endothelial activation and injury likely results in disturbed microcirculation with either increased vascular permeability or vasoconstriction with altered intrinsic vascular tone from platelet aggregation and inflammatory cytokine expression. Enhanced systemic endothelial activation (swelling), leukocyte trafficking and vasoconstriction alone or in combination may result in brain and systemic hypoperfusion.[5] Recently Fugate *et al*.[8] reviewed 120 cases of PRES and found that a substantial proportion of patients had underlying autoimmune conditions, which also supports endothelial dysfunction as a pathophysiological mechanism. Besides eclampsia/pre-eclampsia, these features can be the underlying mechanism in other conditions causing PRES, including infection/sepsis, cancer chemotherapy and cyclosporine neurotoxicity. Therefore, endothelial dysfunction seems to be essential in the pathophysiology of PRES.

LDH is an intracellular enzyme that converts lactic acid to pyruvic acid; elevated levels indicate cellular death and leakage of the enzyme from the cell.[9] Serum LDH levels correlate with endothelial dysfunction and this may function as a predictor.[10,11] In the present study, high serum LDH levels were noted in most patients (59%), especially in eclamptic and pre-eclamptic women. In 3 eclamptic patients with normal MAP, high serum LDH levels were present.

The typical neuroimaging patern of PRES is vasogenic edema with predominant involvement of parieto-occipital lobes.[3] However, some atypical presentations such as frontal lobe, brain stem or basal ganglia involvement, have been described in the last decade.[7,12,13] In the present study, the most commonly affected brain regions on the MRI were the parieto-occipital lobes, but atypical presentations were also present. Cytotoxic edema has been described as a complication of PRES.[14] Longer exposure to etiologic factors may be responsible for this complication.[15] Covarrubias *et al*. reported 6 PRES patients who had high DWI

signal intensity with normal ADC values on cranial MRI, which they called pseudonormalization.[14] They also reported that these patients had the worst outcome. In contrast to Covarrubias *et al*, in the present study, one patient with ischemia and 3 patients witha pseudonormalization pattern on the cranial MRI hada good clinical outcome.

Prior studies have demonstrated parenchymal hematoma or sulcal subarachnoid hemorrhage in 5-17% of patients.[7,4] The mechanism behind hemorrhage is unclear.[4] Doss-Esper *et al*. have proposed two hypotheses; firstly, severe hypertension and impaired cerebral autoregulation causing rupture of pial vessels, and secondly, post-ischemic reperfusion injury leading to multifocal brain hemorrhages.[16] Hefzy *et al*. reported differences in the incidence of hemorrhage between different etiological factors, immunosupressive drug usage having the highest rate (22%) and eclampsia having the lowest rate (5.5%). They also reported that hemorrhage rate was not correlated with blood pressure elevation and clinical outcome was not affected by hemorrhage determination.[17]

Cyclosporine, one of the most commonly used immunosuppressive drugs, can cause direct endothelial injury and inhibit T-cellfunction.[18] It can also induce vasoconstriction by endothelial cell production, release of endothelin and systemic sympathetic stimulation.[19-21] Hypertension caused by systemic/renal vasoconstriction can lead to reduced cerebral blood flow due to autoregulatory vasoconstriction. The combined effects may lead to increased risk of hemorrhage.[17] In their study, Sharma *et al*. found coagulation abnormalities in almost half of patients with hemorrhage, but they also reported that this was not a prerequisite for hemorrhage.[22] Similar observations were made by Hefzy *et al*., who found normal coagulation parameters in 43% of patients with intracranial hemorrhage.[17] In the present study, 3 patients (14%) had cortical hemorrhage in the area of vasogenic edema. One of the two patients with eclampsia had elevated MAP and low platelet count and the other had normal MAP and low platelet count. The third patient using cyclosporine had normal MAP and coagulation parameters. mRS was 0 in those 3 patients, no different from the patients who had no hemorrhage.

MRI lesion locations were analyzed in high MAP, high serum LDH and low serum albumin level groups to detect which factors affect the extent of brain edema. Gao *et al*. found that increased serum LDH levels were significantly correlated withscores of brain edema distribution.[23] Schwartz *et al*. reported that serum LDH levelsin patients with brain edema were significantly higher than those who had normal MR imaging findings.[10] In the present study, no correlation was found between extent of MRI lesions and elevated MAP and/or high serum LDH levels. However, in 12 patients with hypoalbuminemia, MRI lesions showed significant extension. In fact, this finding has been reported in previous studies. These relations are summarized on Table 5. Albumin may be reduced as a consequence of an elevated metabolic turnover, accelerated aging of the molecules through oxidative stress or increased leakage due to immune mediated vasculopathy.[24,25] Albumin is one of the most important plasma antioxidants, scavenging and detoxifying reactive oxigen species (ROS). Excessive production of ROS can lead to hypoalbuminemia and endothelial dysfunction, which can cause disease progression.[25] A possible correlation between low albumin levels and PRES has been discussed by Ishikura *et al*.[26], whoreported 7 pediatric patients with nephrotic syndrome and hypoalbuminemia. In these patients, significant clinical improvement was recorded after albumin replacement.

Small number of patients is one of the limitations of the study. Also there were insufficient MRI data to evaluate factors affecting lesion reversibility. However, the eclamptic patients showed totally reversible lesions. Pande *et al*. reported that eclamptic patients showed maximum reversibility on follow-up MR images compared to patients who had severe hypertension or were on immunosuppressing drugs. They attributed this finding to different pathophysiological mechanisms underlyingthe condition.[27]

Functional outcome of patients with severe PRES was evaluated in a study by Legriel S *et al*.[28] They reported that three factors were associated with the day-90 functional outcome: 1) time to control of the causative factor (the most important factor); 2) highest glycemia on day 1; 3) toxemia of pregnancy (eclampsia/pre-eclampsia). In the present study, the mRS of patients at hospital discharge was 0, except for one patient who died due to septic shock. In the majority of patients, the main etiologic factor was toxemia of pregnancy and median time to causative-factor control was 1 day. In accordance with the study mentioned above, these factors may have played an important role in the good clinical outcome of the patients.

Follow-up MRI of all patients as well as laboratory markers could not be accomplished due to the retrospective nature of the study. Further

studies are needed to clarify the role of these markers in pathopysiology and treatment.

In summary, seizures and loss of consciousness were the most common presenting symptoms in our patients. Although increased MAP is a causitive factor in vasogenic edema as seen in MRI of PRES, approximately 45% of our patients had normal MAP and patients using immunosuppressive agents all had normal MAP. So this finding suggests that other mechanisms causing endothelial dysfunction must be operating. Serum LDH level can increase as an indication of cell damage and this was detected in most of our patients especially in the eclamptic and pre-eclamptic group. In the literature, it is reported that hypoalbuminemia can be a risk factor in diffuse paranchymal involvement and this was the case in our 12 patients who all had hypoalbuminemia. However, we did not find any correlation between the extent of MRI lesions and elevated MAP and/or high serum LDH levels. As mentioned in the literature, early cessation of the causitive factor seem to be important in good prognosis.

In conclusion, in this study, although hypertension is thought to be the main pathologic factor in the disease process, endothelial dysfunction seems to be equally important. Serum LDH levels may function as a predictor of the syndrome in patients with eclampsia/pre-eclampsia. Early control of the causative factor seems to be the most critical factor underlying a good prognosis.

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